RESPONSE UNDER 37 CFR 1.116
EXPEDITED PROCEDURE
EXAMINING GROUP 1615

PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

PARIKH et al.

Application No. 09/281,430 Art Unit: 1615

Filed: March 30, 1999 Examiner: T. Ware

For: ANTICANCER COMPOSITIONS

PENDING CLAIMS AFTER AMENDMENTS
MADE IN RESPONSE TO OFFICE ACTION DATED DECEMBER 18, 2002

26. A storage-stable, self-emulsifying, and non-aqueous, preconcentrate of a taxane in a microemulsion comprising a taxane dissolved in a carrier system, which carrier system consists essentially of:

10 to 80% w/w of a hydrophobic component selected from the group consisting of a triglyceride, a diglyceride, a monoglyceride, a free fatty acid, a fatty acid ester, a fish oil, a vegetable oil, and combinations thereof;

20 to 80% w/w of a surfactant component consisting of one or more non-ionic surfactants;

up to 35% w/w diethylene glycol monoethylether; and

up to 40% w/w of a hydrophilic component selected from the group consisting of a hydroxyalkane, a dihydroxyalkane, a polyethylene glycol having an average molecular weight of at most 1000, and combinations thereof;

wherein the preconcentrate, when mixed with water or simulated gastric fluid, forms a liquid having an average droplet size of at most 10 microns, and a dose of the preconcentrate has a taxane bioavailability of 25 to 60% of the taxane in the dose upon oral administration.

27. The self-emulsifying preconcentrate of claim 26, wherein the carrier system consists of 15 to 75% w/w of the hydrophobic component.

28. The self-emulsifying preconcentrate of claim 26, wherein the carrier system consists of up to 30% w/w of the hydrophilic component.

29. A storage-stable, self-emulsifying, and non-aqueous preconcentrate of at least one taxane in a composition consisting essentially of:

10 to 80% w/w of a hydrophobic component selected from the group consisting of a triglyceride, a diglyceride, a monoglyceride, a free fatty acid, a fatty acid ester, a fish oil, a vegetable oil, and combinations thereof;

20 to 80% w/w of a surfactant component consisting of one or more non-ionic surfactants; and

up to 40% of a hydrophilic component selected from the group consisting of a hydroxyalkane, a dihydroxyalkane, a polyethylene glycol having an average molecular weight of at most 1000, 1,2-propylene glycol, ethanol, and combinations thereof;

wherein the preconcentrate, when mixed with water or simulated gastric fluid, gives an average droplet size of at most 10 microns, and a dose of the preconcentrate has a taxane bioavailability of 25 to 60% of the taxane in the dose upon oral administration.

30. The preconcentrate of claim 29, wherein the hydrophilic component is selected from the group consisting of 1,2-propylene glycol and ethanol.

31. An orally administrable pharmaceutical composition consisting essentially of the preconcentrate of claim 29 in a pharmaceutically acceptable carrier or diluent.

32. A parenterally injectable pharmaceutical composition consisting essentially of the preconcentrate of claim 29 in a pharmaceutically acceptable diluent.

33. The preconcentrate of claim 29 filled in a soft or hard gelatin capsule.

34. The preconcentrate of claim 29, wherein the preconcentrate also includes an inhibitor of P-glycoprotein transport system or an inhibitor of cytochrome P450 enzyme.

35. The preconcentrate of claim 29, wherein the preconcentrate comprises grapefruit extract or a component thereof.

36. The preconcentrate of claim 29, wherein the taxane is paclitaxel or docetaxel.

37. A method of orally or parenterally administering a taxane to a subject in need of same comprising administering a dose of a storage-stable, self-emulsifying, and non-aqueous preconcentrate of a taxane consisting essentially of:

10 to 80% w/w of a hydrophobic component selected from the group consisting of a triglyceride, a diglyceride, a monoglyceride, a free fatty acid, a fatty acid ester, a fish oil, a vegetable oil, and combinations thereof;

20 to 80% w/w of a surfactant component consisting of one or more non-ionic surfactants; and

up to 40% w/w of a hydrophilic component selected from the group consisting of a hydroxyalkane, a dihydroxyalkane, a polyethylene glycol having an average molecular weight of at most 1000, and combinations thereof;

wherein the preconcentrate, when mixed with water or simulated gastric fluid, gives an average droplet size of at most 10 microns, and a dose of the preconcentrate has a taxane bioavailability of 25 to 60% of the taxane in the dose upon oral administration.

38. The method of claim 37, wherein the taxane is solubilized in the preconcentrate.

39. A storage-stable, self-emulsifying, and non-aqueous preconcentrate of a taxane in a microemulsion comprising a taxane dissolved in a carrier system, which carrier system consists essentially of:

10 to 80% w/w of a hydrophobic component;

20 to 80% w/w of a surfactant component consisting of one or more non-ionic surfactants; and

up to 40% w/w of a hydrophilic component.

40. The preconcentrate of claim 39, wherein the preconcentrate forms a liquid having an average droplet size of at most 10 microns when mixed with water or simulated gastric fluid.

41. The preconcentrate of claim 40, wherein a dose of the preconcentrate has a taxane bioavailability of 25 to 60% upon oral administration.

42. The preconcentrate of claim 41, wherein at least a portion of the hydrophilic component consists of ethanol, such that the carrier system contains at least 6% w/w ethanol.

43. The preconcentrate of claim 39, wherein the preconcentrate, when mixed with an aqueous medium and heated to 20-37° C, forms a liquid having an average droplet size of at most 10 microns.

44. The preconcentrate of claim 43, wherein the preconcentrate, upon oral administration, forms a microemulsion *in situ* in the gastrointestinal tract.

45. A storage-stable, self-emulsifying, and non-aqueous preconcentrate of a taxane in a microemulsion comprising a taxane dissolved in a carrier system, which carrier system consists essentially of:

10 to 80% w/w of a hydrophobic component;

20 to 80% w/w of a surfactant component; and

6% to 40% w/w of a hydrophilic component, at least a portion of which hydrophilic component consists of ethanol, such that the carrier system contains at least 6% w/w ethanol.

46. The preconcentrate of claim 45, wherein the surfactant component consists of one or more surfactants selected from the group consisting of polyoxyethylene-sorbitan-fatty acid esters, polyoxyethylene fatty acid esters, α-tocopherol, α-tocopheryl polyethylene glycol succinate, α-tocopherol palmitate, α-tocopherol acetate, PEG glyceryl fatty acid esters, propylene glycol mono- or di-fatty acid esters, sorbitan fatty acid esters, polyoxyethylene-polyoxypropylene co-polymers, glycerol triacetate, monoglycerides, and acetylated monoglycerides.

47. The preconcentrate of claim 46, wherein the preconcentrate forms a liquid having an average droplet size of at most 10 microns when mixed with water or simulated gastric fluid.

48. The preconcentrate of claim 47, wherein a dose of the preconcentrate has a taxane bioavailability of 25 to 60% upon oral administration.

49. The preconcentrate of claim 45, wherein the preconcentrate, when mixed with an aqueous medium and heated to 20-37° C, forms a clear liquid having an average droplet size of at most 10 microns.

50. The preconcentrate of claim 49, wherein the preconcentrate, upon oral administration, forms a microemulsion *in situ* in the gastrointestinal tract.

51. A storage-stable, self-emulsifying, and non-aqueous preconcentrate of a taxane in a microemulsion comprising a taxane dissolved in a carrier system, which carrier system consists essentially of:

10 to 80% w/w of a hydrophobic component selected from the group consisting of a triglyceride, a diglyceride, a monoglyceride, a free fatty acid, a fatty acid ester, a fish oil, a vegetable oil, and combinations thereof;

20 to 80% w/w of a surfactant component consisting of one or more surfactants selected from the group consisting of a polyoxyethylene-sorbitan-fatty acid ester, a polyoxyethylene fatty acid ester, a polyoxyethylene castor oil derivative, α-tocopherol, α-tocopheryl polyethylene glycol succinate, α-tocopherol palmitate, α-tocopherol acetate, a PEG glyceryl fatty acid ester, a propylene glycol mono- or di-fatty acid ester, a sorbitan fatty acid ester, a polyoxyethylene-polyoxypropylene co-polymer, glycerol triacetate, a monoglyceride, an acetylated monoglyceride, and combinations of any thereof; and

6% to 40% of a hydrophilic component, at least a portion of the hydrophilic component consisting of ethanol, such that the carrier system contains at least 6% w/w ethanol.

52. The preconcentrate of claim 51, wherein a dose of the preconcentrate has a taxane bioavailability of 25 to 60% upon oral administration.

53. An injectable pharmaceutically acceptable composition consisting essentially of a storage-stable, self-emulsifying, and non-aqueous preconcentrate of at least one taxane in a composition consisting essentially of:

10 to 80% w/w of a hydrophobic component;

20 to 80% w/w of a surfactant component; and

6% to 40% w/w of a hydrophilic component,

wherein (a) at least a portion of which hydrophilic component consists of ethanol, such that the composition contains at least 6% w/w ethanol, (b) the surfactant component of the composition consists of one or more non-ionic surfactants, or (c) conditions (a) and (b) apply.

54. A storage-stable, self-emulsifying, and non-aqueous, preconcentrate of a taxane in a microemulsion consisting of a taxane dissolved in a carrier system, which carrier system consists of:

10 to 80% w/w of a hydrophobic component selected from the group consisting of a triglyceride, a diglyceride, a monoglyceride, a free fatty acid, a fatty acid ester, a fish oil, a vegetable oil, and combinations thereof;

20 to 80% w/w of a surfactant component consisting of one or more non-ionic surfactants;

up to 35% w/w diethylene glycol monoethylether; and

up to 40% w/w of a hydrophilic component selected from the group consisting of a hydroxyalkane, a dihydroxyalkane, a polyethylene glycol having an average molecular weight of at most 1000, and combinations thereof;

wherein the preconcentrate, when mixed with water or simulated gastric fluid, forms a liquid having an average droplet size of at most 10 microns, and a dose of the preconcentrate has a taxane bioavailability of 25 to 60% of the taxane in the dose upon oral administration.

55. A storage-stable, self-emulsifying, and non-aqueous preconcentrate of at least one taxane in a composition consisting of:

10 to 80% w/w of a hydrophobic component selected from the group consisting of a triglyceride, a diglyceride, a monoglyceride, a free fatty acid, a fatty acid ester, a fish oil, a vegetable oil, and combinations thereof;

20 to 80% w/w of a surfactant component consisting of one or more non-ionic surfactants; and

up to 40% of a hydrophilic component selected from the group consisting of a hydroxyalkane, a dihydroxyalkane, a polyethylene glycol having an average molecular weight of at most 1000, 1,2-propylene glycol, ethanol, and combinations thereof;
wherein the preconcentrate, when mixed with water or simulated gastric fluid, gives an average droplet size of at most 10 microns, and a dose of the preconcentrate has a taxane bioavailability of 25 to 60% of the taxane in the dose upon oral administration.

56. A method of orally or parenterally administering a taxane to a subject in need of same consisting of administering a dose of a storage-stable, self-emulsifying, and non-aqueous preconcentrate of a taxane consisting of:

10 to 80% w/w of a hydrophobic component selected from the group consisting of a triglyceride, a diglyceride, a monoglyceride, a free fatty acid, a fatty acid ester, a fish oil, a vegetable oil, and combinations thereof;

20 to 80% w/w of a surfactant component consisting of one or more non-ionic surfactants; and

up to 40% w/w of a hydrophilic component selected from the group consisting of a hydroxyalkane, a dihydroxyalkane, a polyethylene glycol having an average molecular weight of at most 1000, and combinations thereof;

wherein the preconcentrate, when mixed with water or simulated gastric fluid, gives an average droplet size of at most 10 microns, and a dose of the preconcentrate has a taxane bioavailability of 25 to 60% of the taxane in the dose upon oral administration.

57. A storage-stable, self-emulsifying, and non-aqueous preconcentrate of a taxane in a microemulsion consisting of a taxane dissolved in a carrier system, which carrier system consists of:

10 to 80% w/w of a hydrophobic component;

20 to 80% w/w of a surfactant component consisting of one or more non-ionic surfactants; and

up to 40% w/w of a hydrophilic component.